REMARKS

Claims 2-14, 16, 26-28, 40, 49-61, 63, 72, 86, 94 and 100-141 were pending in this application. In view of their withdrawal from consideration, claims 3, 4, 27, 28, 50 and 51 have been canceled, without prejudice to Applicants' right to pursue the subject matter of the canceled claims in related applications. Applicants have rewritten dependent claims 5, 29 and 52 as independent claims. Applicants have also amended claim 49 to correct grammatical and typographical errors. In particular, claim 49 has been amended to clarify the language of the claim and to add the word "comprising" which was inadvertently omitted from the claim. Applicants have also amended claims 6, 30 and 53 to correct grammatical errors and to add apomigren as an anti-angiogenic factor. Further, Applicants have added new dependent claims 142-188, which depend directly or indirectly from claims 5, 29 or 52. The claim amendments are not narrowing amendments. Support in the specification for the claim amendments and new claims can be found throughout, for example at page 11, line 10 to page 13, line 6; page 13, line 26 to page 14, line 20; page 17, line 36 to page 19, line 4; page 28, line 1 to page 29, line 27; page 32, line 30 to page 33, line 14; page 34, lines 7-19; page 35, line 26 to page 38, line 6; page 44, line 26 to page 47, line 13; and page 63, line 14 to page 66, line 20 of the specification. Thus, Applicants assert that the claim amendments and new claims do not constitute new matter. Upon entry of this amendment, claims 2, 5-14, 16, 26, 40, 49, 52-61, 63, 72, 86, 94 and 100-188 will be pending in the present application, although claims 9-11, 13, 33-35, 37, 56-58, 60, 100-104, 106-117, 119-130 and 132-141 are withdrawn from active consideration.

The cancellation of claims has resulted in less than all of the originally named inventors being actual inventors of the presently claimed invention. Thus, pursuant to 37 C.F.R. § 1.48(b), the application has been amended to delete Stanley Lin as a co-inventor of the application. This amendment is accompanied by a Petition For Correction of Inventorship Under 37C.F.R. § 1.48(b), accompanied by a provision authorizing payment of the required fee.

Entry of the foregoing amendments and consideration of these remarks are respectfully requested.

1. INFORMATION DISCLOSURE STATEMENT

The Office Action asserts that the Information Disclosure Statement ("IDS")

filed on August 24, 2001 fails to comply with 37 C.F.R. § 1.98(a)(1) because a PTO-1449 form or the equivalent, listing all patents, publications, or other information submitted for consideration by the United States Patent and Trademark Office ("USPTO"), was not filed. Applicants respectfully submit that a revised PTO-1449 form and copies of references AA-EZ were, indeed, filed with the IDS on August 24, 2001 in the USPTO using "Express Mail Post Office to Addressee" service under Express Mail Label No. EL 501 638 985 US. As evidence of the fact that a revised PTO-1449 form and copies of references AA-EZ were filed on August 24, 2001 in the USPTO and received by the USTPO, Applicants enclose herewith: (1) Exhibit A, a copy of Express Mail Label No EL 501 638 985 US with the "date-in" August 24, 2001 and "time-in" 19:06; and (2) Exhibit B, a copy of the postcard, which listed on one side the items filed on August 24, 2001 and Express Mail Label No. EL 501 638 985 US, returned to Applicants' attorneys stamped received by the USPTO with the date of August 24, 2001. Accordingly, pursuant to 37 C.F.R. § 1.10(a), Applicants did, indeed, file a revised PTO-1449 form and copies of references AA-EZ with an IDS on August 24, 2001 in the USPTO.

In order to expedite the examination of the present application, Applicants are filing herewith a courtesy copy of the revised PTO-1449 form and IDS filed on August 24, 2001. Applicants respectfully request that the Examiner review and consider references AA-EZ listed on the revised PTO 1449 form enclosed herewith. The Examiner is invited to contact attorneys for Applicants' to obtain copies of references AA-EZ if the Examiner is unable to locate them at the USPTO.

2. THE OBJECTION OF THE DECLARATION AND SPECIFICATION SHOULD BE WITHDRAWN

The specification and the oath/declaration are objected to because the priority information listed in the first sentence of the specification and the priority information listed on the oath/declaration do not match. The first sentence of the specification correctly recites the priority information for the present application. Applicants respectfully assert that the oath/declaration contains typographical errors in the filing dates of the U.S. provisional applications of which the present application claims priority benefits. In particular, the filing dates recited in the oath/declaration for U.S. provisional application Serial Nos. 60/157,637, 60/157,581, and 60/157,500 should be October 4, 1999, not October 4, 2000. Since this application was filed on August 24, 2000, it is clear that the recited date October 4, 2000 is a typographical error in the Declaration. In order to correct the priority information in the

oath/declaration, Applicants have submitted herewith a Supplemental Declaration listing the correct priority information for the present application. Accordingly, Applicants respectfully submit that the objection to the specification and the oath/declaration is moot and thus, should be withdrawn.

3. THE REJECTION UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 2, 5-8, 12, 14, 16, 26, 29-32, 36, 38, 40, 52-55, 59, 61, 63, 105, 118 and 131 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,537,558 to Kaniga ("Kaniga"), U.S. Patent No. 6,410,012 to Sizemore et al. ("Sizemore"), U.S. Patent No. 6,190,657 to Pawelek et al. ("Pawelek") in view of Boehm et al., 1997, Nature 390: 404-407 ("Boehm") and Hakkaart et al., 1981, Mol. Gen. Genet. 183: 326-332 ("Hakkaart"). The Office Action alleges that: (a) Kaniga teaches attenuated bacteria with decreased virulence as a result of a mutation in the regulatory poxR gene and the use of such bacteria as a vaccine, a host for the expression of heterologous genes and proteins, or to deliver DNA to cells; (b) Sizemore teaches a method for delivering a desired functional DNA or antigen to cells using attenuated bacteria; (c) Pawelek teaches super-infective, tumor-specific attenuated strains of bacteria and the use of such bacteria to deliver gene products such as HSV thymidine kinase (HSV-TK) and pro-drug converting enzyme to tumor cells for the treatment of cancer; (d) Boehm teaches treating cancer in mice with the angiogenesis inhibitor TNP470 or endostatin; and (e) Hakkaart "teaches genes encoded by the bacterial plasmid Clo Df13 and that the protein H encoded by the plasmid causes bacterial cell lysis". The Office Action concedes that these references do not teach a bacteria that comprises one or more nucleic acids encoding an anti-angiogenic factor and a bacteriocin release factor. However, the Office Action alleges that it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to modify the bacteria of Kaniga, Pawelek or Sizemore to express an anti-angiogenic factor, such as endostatin, and a factor that helps with the lysis of the bacteria and to use such bacteria for treating cancer. For the reasons detailed below, the rejection cannot stand and should be withdrawn.

A finding of obviousness requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1996). Secondary considerations such as

commercial success, long felt but unsolved needs, and failure of others to solve the problem or make the advance claimed by the patent at issue are to be considered when making a determination on the issue of obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Following *Graham*, the Court of Customs and Patent Appeals (CCPA) and its present successor, the Court of Appeals for the Federal Circuit (CAFC), have held the following considerations to be objective evidence of nonobviousness: long felt need, commercial success, failure of others, copying and unexpected results. *See, e.g., Avia Group Int'l Inc. v. L.A. Gear California, Inc.*, 853 F.2d 1557, 7 U.S.P.Q.2d 1548 (Fed. Cir. 1988); *In re Sernaker*, 702 F.2d 989, 217 U.S.P.Q. 1 (Fed. Cir. 1983). The proper inquiry is whether the prior art suggests the invention, and whether the art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell* 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicants' disclosure. *In re Vaeck* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Obviousness "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination", and "teachings of references can be combined only if there is some suggestion or incentive to do so." *In re Fine* 837 F.2d 1071, 1075.

Neither Kaniga, Sizemore, Pawelek, Boehm nor Hakkaarat alone or in combination, teach, suggest or provide a motivation to one of skill in the art to produce an attenuated tumor-targeted bacteria comprising one or more nucleic acid molecules encoding an anti-angiogenic factor, such as endostatin, and a bacteriocin release protein ("BRP"), much less a pharmaceutical composition comprising such bacteria or a method of delivering an anti-angiogenic factor and a BRP to treat a solid tumor cancer by administering such bacteria.

Kaniga describes bacteria attenuated by a mutation in the regulatory gene poxR and the use of such bacteria as delivery systems to deliver a gene product, such as an antigen, to stimulate an immune response. Kaniga does not contemplate, teach or suggest attenuated tumor-targeted bacteria, *i.e.*, bacteria that preferentially attach to, infect and/or remain viable in a cancerous target cell or a tumor environment, much less attenuated tumor-targeted bacteria comprising one or more nucleic acids encoding a primary effector molecule, such as an anti-angiogenic factor, and a secondary effector molecule, such as a BRP. Kaniga only describes bacteria attenuated by a mutation in the regulatory gene poxR. Moreover,

Kaniga focuses on the delivery of antigens by bacteria having a mutation in poxR that are engineered to express such antigens. In particular, in the context of halting cancer, Kaniga describes the delivery of tumor-antigens by bacteria having a mutation in poxR that are engineered to express such tumor-antigens. See Kaniga at col. 10, line 68. Thus, even with respect to the poxR mutant bacteria described by Kaniga, Kaniga does not contemplate, teach or suggest engineering the bacteria to encode a primary effector molecule (*i.e.*, members of the tumor necrosis factor ("TNF") family, anti-angiogenic factors such as endostatin, cytotoxic polypeptides or peptides, tumor inhibitory enzymes and functional fragments thereof) and a secondary effector molecule, such as a BRP.

Sizemore describes methods of delivering DNA or antigens to cells using attenuated bacteria. Sizemore does not contemplate, teach or suggest attenuated tumor-targeted bacteria, *i.e.*, bacteria that preferentially attach to, infect and/or remain viable in a cancerous target cell or a tumor environment, much less attenuated tumor-targeted bacteria comprising one or more nucleic acids encoding a primary effector molecule, such as an anti-angiogenic factor, and a secondary effector molecule, such as a BRP. Rather, Sizemore only generically describes attenuated bacteria. See Sizemore at col. 4, lines 54-64. Moreover, the focus of Sizemore is the delivery of DNA to cells by lysing attenuated bacteria inside the cells to release the DNA that they have been engineered to contain. In the context of the delivery of antigens, Sizemore only mentions in passing the use of attenuated bacteria engineered to express foreign antigens to deliver of heterologous foreign antigens for the purpose of inducing an immune response against the foreign antigen or for the treatment of a disease wherein the foreign antigen is missing or found in a reduced amount. See Sizemore at col. 3, lines 42-49. Thus, even with respect to the attenuated bacteria generically described by Sizemore, Sizemore does not contemplate, teach or suggest engineering the bacteria to encode a primary effector molecule (*i.e.*, members of the tumor necrosis factor ("TNF") family, anti-angiogenic factors such as endostatin, cytotoxic polypeptides or peptides, tumor inhibitory enzymes and functional fragments thereof) and a secondary effector molecule, such as a BRP.

Pawelek does not describe engineering attenuated tumor-targeted bacteria to encode a primary effector molecule (*i.e.*, members of the tumor necrosis factor ("TNF") family, anti-angiogenic factors such as endostatin, cytotoxic polypeptides or peptides, tumor inhibitory enzymes and functional fragments thereof) and a secondary effector molecule, such as a BRP. The focus of Pawelek is the delivery of a suicide gene, such as a pro-drug

converting enzyme, to tumor cells using attenuated tumor-targeted bacteria engineered to encode such suicide gene. See Pawelek at col. 18, lines 27-53. Pawelek provides successful methods for treating solid tumor cancers using attenuated tumor-targeted bacteria. Thus, one of skill in the art would not have been motivated to engineer attenuated tumor-targeted bacteria encoding a primary effector molecule (*i.e.*, a member of the tumor necrosis factor ("TNF") family, an anti-angiogenic factor such as endostatin, a cytotoxic polypeptide or peptide, a tumor inhibitory enzyme or a functional fragment thereof) and a secondary effector molecule, such as a BRP, for treating solid tumor cancers.

The deficiencies of Kaniga, Sizemore and Pawelek are not cured by Boehm and Hakkaart. Boehm describes treating mice bearing Lewis lung carcinoma, T241 fibrosarcoma and B16F10 melanoma with purified endostatin protein. Boehm suggests the use of anti-angiogenic factors, such as purified endostatin protein, in combination with conventional anti-cancer therapies such as surgery, chemotherapy, radiotherapy or immunotherapy. There is no teaching or suggestion in Boehm to introduce nucleic acids encoding an anti-angiogenic factor, much less engineering bacteria to express nucleic acids encoding an anti-angiogenic factor. Boehm does not contemplate, teach or suggest attenuated bacteria, much less attenuated tumor-targeted bacteria comprising one or more nucleic acids encoding a primary effector molecule, such as an anti-angiogenic factor, and a secondary effector molecule, such as a BRP.

Hakkaart teaches that the expression of protein H by the plasmid Clo DF13 results in lysis of bacterial cells. Hakkaart does not contemplate, teach or suggest attenuated bacteria, much less attenuated tumor-targeted bacteria comprising one or more nucleic acids encoding a primary effector molecule, such as an anti-angiogenic factor, and a secondary effector molecule, such as a BRP.

The combination of Kaniga, Boehm and Hakkaart does not teach or suggest the claimed invention. In particular, the combination of Kaniga, Boehm and Hakkaart does not teach or suggest attenuated tumor-targeted bacteria, much less engineering attenuated tumor-targeted bacteria to encode a primary effector molecule, such as an anti-angiogenic factor (*e.g.*, endostatin), and a secondary effector molecule, such as BRP. Moreover, there is no teaching or suggestion supplied by Kaniga, Boehm or Hakkaart to combine these references.

Sizemore in combination with Boehm and Hakkaart does not teach or suggest

the claimed invention. In particular, the generic teaching in Sizemore regarding attenuated bacteria engineered to deliver DNA or foreign antigens combined with the teaching in Boehm regarding the effect of the administration of purified endostatin protein on tumor growth in mice and the teaching in Hakkaart regarding the lytic effect of protein H encoded by the plasmid Clo DF13 does not result in the claimed invention. Moreover, there is no teaching or suggestion supplied by Sizemore, Boehm or Hakkaart to combine these references.

Pawelek in combination with Boehm and Hakkaart does not teach or suggest the claimed invention. Moreover, one of skill in the art would not be motivated to combine Pawelek with Boehm and Hakkaart to produce an attenuated tumor-targeted bacteria comprising one or more nucleic acids encoding a primary effector molecule, such as endostatin, and a secondary effector molecule, such as BRP, because one of skill in the art would reasonably expect that the lytic activity of a secondary effector molecule such as BRP would interfere with the ability of the bacteria to target the tumor site.

Thus, the combination of Kaniga, Sizemore or Pawelek and Boehm and Hakkaart do not teach or suggest the attenuated tumor-targeted bacteria, the pharmaceutical compositions or the methods of the claimed invention. Accordingly, a *prima facie* case of obviousness has not been established.

Assuming, *arguendo*, that a *prima facie* case of obviousness were established, Applicants may point to surprising and unexpected results to in order to rebut the same and demonstrate nonobviousness. *In re Chupp* 816 F.2d 643, 2 U.S.P.Q.2d 1437 (Fed. Cir. 1987). Applicants invite the Examiner's attention to the Examples presented in the present application, in particular, Example 13 which describes the successful inhibition of tumor growth using attenuated tumor-targeted bacteria engineered to express endostatin and BRP (see pages 81-84 and Figures 17 and 18 of the present specification). Applicants discovered that the expression of both endostatin and BRP significantly increased tumor inhibition relative to attenuated tumor-targeted bacteria expressing endostatin and attenuated tumor-targeted bacteria harboring an empty vector (see page 83, lines 16-35 and Figure 17 of the present specification). These results are surprising because one of skill in the art would not expect that the expression of BRP, a protein with lytic activity, would be compatible with the attenuated tumor-targeted bacteria and thus, increase the tumor inhibition by attenuated bacteria engineered to express endostatin. Accordingly, producing attenuated tumor-targeted bacteria comprising one or more nucleic acids encoding endostatin and BRP and using such bacteria to treat cancer would not have been obvious to one of skill in the art at the time the

invention was made.

In view of the foregoing, the rejection under 35 U.S.C. § 103(a) cannot stand and should be withdrawn.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. Applicants believe that all of the present claims meet all the requirements for patentability. Withdrawal of all rejections and reconsideration of the amended claims are requested. An allowance is earnestly sought.

If any issues remain, the Examiner is requested to telephone the undersigned at (212) 790-2296.

Respectfully submitted,

Date: October 14, 2003

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